REMARKS

Claims Status

Claims 1-42 were pending in the present application. The Examiner states that Claims 1-44 are pending in the subject application, however 42 total claims were presented in the Preliminary Amendment filed June 6, 2006 and in the Amendment filed December 11, 2008. Clarification is sought by Applicants.

Applicants hereby cancel claims 2-4, 22-34 and 37-42 without prejudice to pursue canceled subject matter in a future divisional or continuation application. Applicants hereby amend claims 11 and 16-21 to correct typographical errors and/or provide clarity and consistency in defining the present invention that the Applicants deem as theirs. Support for the amendments to claims 11 and 17 are found in the specification at, e.g., page 13, line 9. Support for the amendments to claims 16 and 18-21 are found in the specification at, e.g., page 19, line 32 through page 20, line 5, and in original claim 1. No new matter has been added.

Upon entry of this amendment, claims 1 and 12-17 will be pending and under examination. Claims 5-11, 18-21 and 35-36 were withdrawn from consideration.

Election/Restrictions

The Examiner has maintained restriction for examination purposes. Should the Examiner find the elected product claims allowable, Applicants respectfully request that the product claims (pharmaceutical composition claims 1 and 12-17, i.e. Examiner's Group I) and remaining process claims (method claims 5-11, 18-21 and 35-36, see e.g., Examiner's Group IV) be rejoined and fully examined in accordance with 37 C.F.R. §1.104. See MPEP §821(a).

Rejection under 35 USC §103

The Examiner rejects claims 1 and 12-17 as allegedly being unpatentable over Tollefson et al (EP0966967), in view of Morisset et al (JPET, 1999, Vol. 288(2): 590-596), further in view of

Leurs et al (TiPS, May 1998, Vol. 19:177-183), and further in view of Schlicker and Kathmann (Euro Neuropsychopharm, Sept. 2000, Vol. 10(3): S199-S200, Abstract S.24.02).

Applicants traverse the rejection and respectfully request reconsideration thereof. The obviousness determination turns on underlying factual inquiries involving: (1) the scope and content of prior art, (2) differences between claims and prior art, (3) the level of ordinary skill in pertinent art, and (4) secondary considerations.

(1) The scope and content of prior art

Tollefson describes compositions for the treatment of bipolar disorder, bipolar depression and unipolar depression. Tollefson's compositions comprise an atypical antipsychotic, and *either* an SRI, an anticonvulsant or lithium. Clozapine and olanzapine are described in the class of atypical antipsychotics. Tollefson et al neither teaches nor implies that clozapine and olanzapine have H3 receptor antagonist properties.

Morrisett et al. investigated many properties of the atypical antipsychotics, clozapine and olanzapine, including those relating to H3 receptor activity. As per Morrisset et al., clozapine and olanzapine are very weak H3 receptor antagonists having 1 and 50 μM Ki values, respectively, and accordingly do not fall within the meets and bounds of Applicants' claimed invention. According to the prior art as a whole, clozapine and olanzapine's weak activity at the H3 receptor is inconsequential to its other, more relevant, binding and, thus, therapeutic properties. Although the Examiner points out a finding by Morisset that clozapine and olanzapine induce "double the steady-state levels of tele-methyl histamine (t-MEHA) levels in the brain", this property of elevated histamine levels in neither relevant nor analogous to the claimed invention because the claimed invention relates to enhanced serotonin levels in the brain and a significant enhancement of SRI activity. In fact, Morrisset concludes that "…despite these observations [increased t-MEHA levels], several findings led us to the conclusion that this effect could not be ascribed to blockade of H3 receptors." (Emphasis added.) See Morisset, page 593, last paragraph. Besides discussion of enhanced histamine levels, the paper discusses dopamine and

its therapeutic potential in schizophrenia, but discusses neither serotonin enhancement nor blockade.

Morisset further offers that "...activation of histaminergic neurons by clozapine (and other antipsychotics) is entirely attributable to 5-HT2A receptor blockade, and that, even at the highest clozapine dosage, H3 receptor blockade does not even contribute." If anything, Tollefson, in view of Morisset, leads the skilled person away from compositions comprising potent H3 antagonists in combination with an SRI, because Morisset's observations do not attribute the therapeutic activity of clozapine and olanzapine to their interaction with the H3 receptor at all. At best, the authors suggest that the additional H3 interaction lends a "positive functional role attributed to HA neurons in processes such as wakefulness, attention, and cognition" (Morisset page 595, last paragraph), but no suggestion is made with regard to H3 activity having a role in anxiety, depression or other affective disorders.

Leurs et al. describes therapeutic potential of H3 receptor agonists and antagonists. Leurs concludes (see page 182, Concluding remarks) that H3 antagonists are interesting candidates for several CNS disorders, however none of the mentioned disorders are related to anxiety or depression. Leurs does not make up for the deficiencies of Morisset and Tollefson.

Schlicker and Kathmann describes that H3 receptor activation *inhibits the release* of 5-HT. Despite the Examiner's belief that motivation comes from explicitly from the reference (see the Office Action at page 7, line 17, the Examiner has misunderstood that H3 antagonist compounds and activator compounds differ, and *inhibiting the release of 5-HT* does not equate to *increased levels of 5-HT*. In fact, Schlicker teaches that "[t]he possibility that effects of the H3-receptor antagonists on the release of serotonin, dopamine and noradrenaline contribute to the behavioural responses is not so very likely since, at least under in vitro conditions, H3-receptor antagonists (although increasing histamine release; Arrang et al.1983) usually failed to affect the release of the three monoamines." (Emphasis added.)(See Schlicker and Kathmann, Abstract S.24.02, second paragraph, last line.)

(2) Differences between the claims and the prior art

The subject claims relate to a pharmaceutical composition comprising one compound, wherein the compound is a serotonin reuptake inhibitor, and a second compound, wherein the second compound is a H_3 receptor antagonist, inverse agonist or partial agonist having an affinity for the H_3 receptor below 0.5 μM. The present application focuses only on compounds that have SRI activity and are high affinity binding H3 antagonists. The prior art does not teach this particular combination and the evidence relied on by the Examiner does not reasonably support a rejection of obviousness. The prior art as a whole does not give any reason to predict that the claimed pharmaceutical composition will have properties in combination that function more effectively when combined, as compared to the function of the compounds when separately administered for their intended purpose.

Leurs et al.'s teachings actually contrast with the claimed invention, because Leurs describes that H3 receptors *inhibit the release* of 5-HT in rat hypothalamus, rather than stimulate or increase extracellular levels of 5-HT in the brain as taught in Applicants' specification. Leurs then asserts that "histamine H3 receptor ligands do not substantially affect brain noradrenaline, dopamine or 5-HT levels *in vivo*." (See Leurs et al. page 179, Box 1, lines 29-31.) No teaching in Leurs would lead one skilled in the art to combine an H3 receptor antagonist with an SRI.

As discussed *supra*, the teachings of Schlicker and Kathmann do not make up for the inadequacies of Leurs because Schlicker describes that although H3 receptor antagonists increase histamine release, the effect of H3 receptor antagonists on monoamine release is not so very likely. (See Schlicker and Kathmann, Abstract S.24.02, second paragraph, last line.)

Given that the cited art *teaches away* from any H3 receptor mechanism contributing to serotonin neurotransmitter release in the brain, Applicants' invention can not be envisioned. The cited references neither teach Applicants' composition, nor do the references teach the same biological activities proposed by Applications' invention and therefore do not support a finding of obviousness.

Based on the prior art as a whole, it is implausible that a person skilled in the art would be motivated to make a composition comprising a potent H3 antagonist and an SRI.

(3) Level of ordinary skill in the pertinent art

The level of ordinary skill in the art of neurobiology and neuroscience is high. The level of skill in the particular art to which the subject application pertains may be reflected in the prior art itself (see the Introductions of Morisset et al, Leurs et al, and Schlicker et al), in which the artisan tries to elucidate various pharmacological interactions involving neurotransmitters, especially bioamines, in the brain in order to provide pharmaceutical treatments. For instance, Morisset explains that atypical antipsychotics were a choice treatment for schizophrenia, replacing the first generation "typical" antipsychotics, and a common property of all antipsychotics is blocking dopamine receptors (page 590, lines 13-14).

As of the filing date of the subject application, several SRIs were known for treating depression, and acted by inhibiting the serotonin reuptake system, which is particularly effective at increasing the level of serotonin (5-HT) in the brain's synaptic terminals. See the background of Applicants' specification. While SRIs are effective in increasing available terminal 5-HT, there may be a delay. The aim of creating more efficacious pharmaceuticals is therefore to enhance the amount of available 5-HT within the extracellular space (outside the synapses of neurons).

The general knowledge in the art does not suggest to the skilled person that H3 antagonists would improve the efficacy of an SRI by elevating 5-HT levels. Furthermore, each cited reference fails to provide motivation to the skilled person. Neither explicit nor implicit teachings lead the skilled person to a predictable outcome or operability for the claimed combination.

(4) Secondary considerations

Applicants unexpectedly discovered that administration of both an SRI *and* a high-affinity H_3 receptor antagonist, inverse agonist or partial agonist, in contrast to the administration of one drug alone, significantly elevates serotonin (5-HT) levels in the brain, as measured *in vivo*. (See, e.g., page 19, lines 1-4 of the subject application.) The evidence presented therein supports

unexpectedly improved properties for the composition. Moreover, the composition does not merely perform the same function as each separate element, but functions in a synergistic manner. For instance, the present application discloses that a high-affinity H_3 receptor antagonist alone does not induce any effect on serotonin levels. Yet the effect of the combination is greater than with the SRI alone. See the specification at page 28, line 5 through page 30, line 15.

In view of the foregoing, Applicant hereby submits the Declaration of Connie Sánchez Morillo pursuant to 37 C.F.R. 1.132, providing further evidence that the claimed invention is not obvious. Dr. Sánchez Morillo points out that the combination of an H3 receptor antagonist, inverse agonist or partial agonist and a serotonin reuptake inhibitor (SRI) elicits an unexpected synergistic effect on the central nervous system, and that this effect could not be obvious, in view of the evidence presented therein.

The resulting elevation in serotonin levels is *far greater than* additive- it is considered synergistic because the addition of 1) the zero increase above baseline 5-HT caused by the H3 antagonist and 2) the 500% above baseline increase of the SRI, 3) would equal the same 500% above baseline increase due to the SRI. However, the combination of the H3 antagonist and the SRI induce 5-HT levels at or above 900% of baseline. See Exhibits B and C which illustrate the data also disclosed in the specification at page 29, line 29 through page 30, line 15. See Dr. Sanchez Morillo's explanation in paragraph 7 of the 1.132 Declaration.

Furthermore, Dr. Sánchez Morillo concludes that given the prior art teachings, one skilled in the art would not conclude that the claimed combination would elicit such a synergistic effect. Thus, the cited references, either alone or combined, fail to suggest predictability or any reasonable expectation of success.

In light of the deficiencies of the prior art teachings and the unexpected synergism of the combination, Applicants respectfully request withdrawal of the rejection under 103(a).

4. Conclusion

For the foregoing reasons, Applicants believe that the application is now in condition for allowance. Such action is earnestly solicited.

The Office is invited to contact the undersigned if an interview would facilitate allowance of the claims. The Commissioner is hereby authorized to charge any fee, or underpayment thereof, or credit any overpayment to deposit account no. **503201**.

Respectfully submitted,

/Stephen G. Kalinchak Reg.# 38,747/

Stephen G. Kalinchak
Registration No. 38,747

Lundbeck Research USA, Inc.
215 College Road
Paramus, New Jersey 07652
(201) 350-0781 (direct)
(201) 225-9571 (fax)